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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	13

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,330	TRAVIS ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 25-30* is/are rejected.

7)☐ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

During a telephone conversation with Mr. Loren D. Albin on May 27, 2003, a provisional election had been made to prosecute the invention of Group 1, claims 1-29 herein. Because the subject matter of claim 30, the remaining restricted claim, is disclosed to be among the inhibitors stated at page 14, lines 8-12, of the specification, and is also disclosed in the prior art made of record with Applicant's Information Disclosure Statement, the requirement for restriction is hereby RESCINDED and all pending claims, i.e., claims 1-30, are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 and 25-29 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the subject matters of the non-specific polypeptides or divergent proteases, or analogs or fragments thereof, of claims 1-20, a composition of claim 29 comprising same, a nucleic acid of claims 21-23, 25, and 26 that encodes a non-specific polypeptide or a divergent protease, or analogs or fragments thereof, or a method of claims 27 and 28 of using an unspecified polypeptide in an assay comprising incubating the polypeptide with a serpin in the presence of prospective protease inhibitors. The rejected claims reach, e.g., claim 15, generic proteins differing at as many as 202 positions, 48% of the positions, among the 482-amino acid sequence of a heavy chain fragment of a mature cysteine protease of *Porphyromonas gingivalis* having the amino acid sequence set forth in SEQ ID NO:1, from positions 148 through 629, inclusive, and reach as well, e.g., claim 14, , generic proteins differing at as many as 438

positions, 67% of the positions, among the 696-amino acid sequence of a mature cysteine protease of *Porphyromonas gingivalis* having the amino acid sequence set forth in SEQ ID NO:1, from positions 148 through 843, as well as nucleic acids encoding such analogs of fragments of, and analogs of, the mature protease, compositions comprising same, and an assay method that utilize the analogs of fragments of, and analogs of, the mature protease.

Yet neither the claims nor the specification describe any cysteine protease capable of functioning as such in the absence of an association with its native light chain region from positions 630-843 of SEQ ID NO:1, inclusive, nor capable of functioning as an analog having a divergent amino acid sequence, nor functioning as a heavy chain fragment without its light chain. The specification nowhere suggests the locations in the sequence of SEQ ID NO:1 wherein amino acid sequences alterations might occur, or what they might be. The specification does not otherwise disclose or suggest the nature or source of such generic proteins, and their fragments, that meet the functional limitations of the claims. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification fails to provide any relevant identifying characteristics of a cysteine protease that exhibits the recited serpin cleaving activity and diverges at as many as 438 amino acid positions from the amino acid sequence set forth from position 148 through position 843, inclusive, of SEQ ID NO:1, nor does it identify any characteristics that will permit a correlation between undisclosed structures of any protein among the myriad species of generic proteins of claims 1-20 and the disclosed amino acid sequence of SEQ ID NO:1.

In addressing the issue of whether a disclosure of a molecular structure of a disclosed polypeptide of one biological species could adequately describe the molecular structure of

a functionally similar, but undisclosed, species of molecule, the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, the claims rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace other, as yet unknown, cysteine proteases defined primarily by the functional limitations of the rejected claims, i.e., the intended results of inventions not made. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of these undisclosed generic proteins to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the generic proteases of claim 1-20, present in a composition of claim 29 and used in methods of claims 27 and 28, or the generic, encoding, nucleic acids of claims 21-23, 25, and 26.

Claims 1-23 and 25-29 are rejected under 35 U.S.C. §112, first paragraph, because the specification is not enabling for any embodiment of bacterial protease having an amino acid sequence that diverges from the amino acid sequences of any of SEQ ID NO:1 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 67%, or even 48%, of the 696 amino acid positions of SEQ ID NO:1 from position 148 through position 843, inclusive. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

Claims 1-29 contemplate arbitrary assignments of any or all amino acid substitutions, additions, or deletions in the disclosed amino acid sequence of a mature cysteine protease

at as many as 48% of the amino acid positions in its 696-amino acid primary structure set forth in SEQ ID NO:1 from position 148 through position 843, inclusive. The rejected claims embrace cysteine proteases, and even generic polypeptides having a desired activity, wherein the native sequence of disclosed in SEQ ID NO:1 from position 148 through position 843, inclusive, is altered so as to produce an undisclosed variant thereof, or truncated to yield a fragment thereof, which in claim 15 may be a variant of a fragment. The specification fails to show that a heavy chain cysteine protease having the amino acid sequence from position 148 through position 629 of SEQ ID NO:1, a "fragment" of the mature protease, retains the recited "amidolytic activity for cleavage" of a non-denatured serpin. Indeed, the only active protease disclosed to have a recited "amidolytic activity for cleavage" of a non-denatured serpin comprises the heavy chain in association with the light chain. See pages 27-37 and 40 of the specification, disclosing, page 31, that the isolated heavy chain is capable of hydrolyzing only collagen.

This rejection is stated under the first paragraph of the statute because the specification cannot support introduction of 438 amino acid sequence alterations in the native sequence of disclosed in SEQ ID NO:1 from position 148 through position 843, inclusive, satisfying the statistical limitation of 37% identity, or even 334 amino acid sequence alterations within SEQ ID NO:1 from position 148 through position 843, inclusive, satisfying the statistical limitation of 52% identity over both the heavy and light chain regions, where amino acid insertions, deletions, or substitutions occur anywhere, in any combination or any pattern, in the mature protease amino acid sequence of 696 amino acids set forth in SEQ ID NO:1. Indeed, neither the prior art of record herein nor Applicant's specification can identify, taken together, 334 amino acids in the native amino acid sequence of SEQ ID NO:1 from position 148 through position 843, inclusive, that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide

to function as a protease having "amidolytic activity for cleavage" for any non-denatured serpin, or to predict the nucleotide sequence of polynucleotides encoding such divergent proteases. While the specification suggests that the artisan might use the nucleic acid sequence of SEQ ID NO:2 to screen and find bacterial chromosomal fragments that encode proteases having the recited activity, there is no guidance in the specification to aid the artisan in identifying the structural characteristics that permit the amidolytic cleavage of serpins and the claims also describe "polypeptides" and "proteases" designed by a person. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent protease enzymes and provide the public with a nucleotide sequence encoding an enzyme that retains the recited function of amidolytic cleavage of serpins.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992)

(functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands, supra*, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of the native protease of SEQ ID NO:1, from position 148 through position 843, inclusive, to the extent recited in the claims,

b) the specification lacks working examples wherein the amino acid sequence of the native protease of SEQ ID NO:1, from position 148 through position 843, inclusive, is altered to the extent recited in the claims,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of bacterial cysteine proteases represented by amino acid sequence of SEQ ID NO:1 have had even a few amino acids specifically identified for concurrent modification.

Thus the scope of subject matters embraced by the phrase, "greater than 52%" identical to, is unsupported by the present specification even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is ambiguous in reciting the phrase, "which cleaves a target polypeptide nonspecifically", because the artisan cannot know what a "target" polypeptide might be save by reference to claim 11, from which claim 16 depends, but claim 16 recites a specific region for cleavage activity: "a reactive site loop region" of a serpin. Clearly, serpins are target polypeptides but claim 16 does not indicate that serpins are cleaved anywhere or what the nature of further "target" polypeptides might be.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 30 is rejected under 35 U.S.C. §102(b) as being anticipated by Burdavari et al., 1996, **THE MERCK INDEX**, "Leupeptins", at page 932, made of record with Applicant's Information Disclosure Statement.

The disclosure of Burdavari et al. anticipates the subject matter of claim 30 because Burdavari et al. disclose the amino acid sequences and modifications of two leupeptins, leupeptin Ac-LL and leupeptin Pr-LL, and because the present specification discloses, see page 14, lines 8-12, and Table II at page 36, that the *Porphyromonas gingivalis* cysteine protease having the amino acid sequence of SEQ ID NO:1 is inhibited by leupeptin.

Claims 21-23, 25 and 26 are rejected under 35 U.S.C. §102(e) as being anticipated by Ross, U.S. Patent No. 6,444,799, made of record herewith.

The U.S. Patent to Ross ('799) issued on a U.S. utility application and is available as prior art under 35 U.S.C. §102(e) to an invention described by claims 21-23, 25 and

26 herein in view of its December 23, 1998, filing date. Claims 21-23, 25 and 26 herein are anticipated because Ross ('799) discloses, in SEQ ID NO:473, a copy of which is attached to the patent, a genomic nucleic acid sequence of *Porphyromonas gingivalis* that encodes a polypeptide having an amino acid sequence of 684 amino acids and that shares complete identity with the cysteine protease amino acid sequence of SEQ ID NO:1 herein at positions 1 through 684, inclusive. The encoded protease is also identical in its internal region from position 184 through position 629 of SEQ ID NO:1, shares 81.1% with the entire amino acid sequence of SEQ ID NO:1, and shares 77.2% identity with the mature protease of SEQ ID NO:1 having an amino acid sequence from position 184 through 843 comprising both heavy and light chain domains. In view of the specification's assertions, and the assertion in claims 11 and 15, that a fragment of the proprotease of SEQ ID NO:1 comprising the heavy chain region of SEQ ID NO:1, positions 184 through 629, exhibits the amidolytic activities of claims 1, 8 and 11, the nucleic acid sequence of SEQ ID NO:473 of Ross encodes a fragment or analog of the mature protease of SEQ ID NO:1 that inherently exhibits amidolytic activities required by claims 1, 8 and 11, and clearly anticipates the subject matters of claims 21-23, 25 and 26. The patent to Ross ('799) does not disclose the isolation or recombinant production of any *Porphyromonas gingivalis* polypeptide, thus cannot anticipate subject matters of claims 1-20 and 29.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37

CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 1-20 and 29 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ross, U.S. Patent No. 6,444,799, discussed above.

The disclosures of Ross ('799), discussed above, are taken as before. Ross ('799) teaches, see col. 2 at lines 45-57, col. 3, lines 3-13, col. 4, lines 21-58, col. 5, lines 16-35, and col. 7, line 23, through col. 8, line 28, that polypeptide-encoding regions of disclosed *P. gingivalis* chromosomal DNA sequences should be incorporated in plasmid expression vectors, wherein they should be placed in operable linkage with a host-specific promoter, and the expression vectors used to transform host cells commonly employed in the art for the recombinant production of heterologous polypeptides, and the recombinant expression of encoded *P. gingivalis* polypeptides induced in such transformed host cells, followed by recovery of encoded *P. gingivalis* polypeptides from the host cells to prepare immunogenic compositions comprising the encoded *P. gingivalis* polypeptides in order to vaccinate animals and raise antibodies diagnostic of *P. gingivalis*, a well-known oral pathogen. Ross ('799) further teaches sources of suitable vectors, promoters, and host cells, as well as techniques for their use, all well known in the art at col. 5, lines 1-14. It would have been obvious to one of ordinary skill in the art at the time the invention was made to recombinantly express the 684-amino acid polypeptide encoded by SEQ ID NO:473 of Ross ('799) by inserting the region encoding the polypeptide in a plasmid expression vector operably-linked to a host-specific promoter, transforming a host cell, inducing expression of the polypeptide, lysing the cell and recovering the polypeptide, and then incorporating the polypeptide, which inherently will have the properties recited in claims 1-20, in an immunogenic composition of claim 29 in order to vaccinate animals and raise antibodies to the polypeptide. This is because Ross ('799) expressly teaches both the encoding nucleic acid sequence and the desirability of recombinantly producing its

encoded polypeptide in order to prepare compositions useful in making antibodies diagnostic for *P. gingivalis*, and provides the artisan ample incentive to do so by teaching that *P. gingivalis* is a well-known oral pathogen.

Claims 27 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ross, U.S. Patent No. 6,444,799, discussed above, and Madden et al., *1995*, **Infection and Immunity**, Vol. 63, pages 238-247, in view of Chen et al., *1992*, **The Journal of Biological Biochemistry**, Vol. 267, pages 18896-18901, and Nelson et al., *1998*, **Analytical Biochemistry**, Vol. 260, pages 230-236, the latter three publications made of record with Applicant's Information Disclosure Statement.

The disclosures of Ross ('799), discussed above, are taken as before, in particular the *P. gingivalis* genomic nucleic acid sequence set forth in SEQ ID NO: 473 therein and the suggestion and guidance of Ross ('799) to produce each polypeptide encoded by a gene of *P. gingivalis* recombinantly. Madden et al. teach the deduction of the PrtT gene product amino acid sequence of *P. gingivalis* from its encoding amino acid sequence, Figure 2 at pages 240-241, and identify the polypeptide product as a cysteine protease, see Figure 7 at page 245, on the basis of regional sequence homologies with the active site regions of several prokaryotic and eukaryotic cysteine proteases, noting, page 242, that "[w]hen aligned with the active center of other cysteine proteases, striking conservation was bound at the reactive cysteine, histidine, and glutamine residues." Madden et al. further teach, pages 245-246 that these regional sequence homologies adequately distinguish the PrtT cysteine protease from other *P. gingivalis* cysteine proteases – the PrtH product, porphyain and two gingipain isoforms – yet establish its similarity to the *tpr* gene's cysteine protease product almost entirely on the basis of the regional sequence homologies around the reactive, active site, residues. See also Fig. 7 at page 245. Madden et al. also teach, page 246, that other cysteine proteases of *P. gingivalis* whose amino acid sequences had not yet been determined include a protease "able to degrade collagens, [complement component] C3, [ ] fibrinogens, fibronectin, [the serpin] α_1-antitrypsin [and several other specific human polypeptides]". Chen et al. teach, see Table IV and discussion of "Inhibition

Spectrum" spanning pages 18898 through 18900, a method of assaying several protease inhibitors to identify inhibitors of a cysteine protease of *P. gingivalis* and further teach, page 18900, that the cysteine protease "can degrade α_1 proteinase inhibitors", all serpins. Nelson et al. teach the use of the α_1-proteinase inhibitor, a serpin, in an assay, see Fig. 1 at page 231, to detect the anti-host defense proteolytic activities of *P. gingivalis* proteases, including a vesicular protease that cleaves the α_1-proteinase inhibitor in a non-denatured state at its reactive site loop region, Fig. 2 at page 233, and which may include cysteine proteases: compare Table 2 at page 235 of Nelson et al. and Fig. 7 of Madden et al., where several cysteine proteases in Table 2 of Nelson et al. capable of cleaving the reactive site loop region of the α_1-proteinase inhibitor have active site regions are represented in Fig. 7 of Madden et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine that a cysteine protease is the product present in the deduced amino acid sequence of the polypeptide encoded by the *P. gingivalis* genomic DNA sequence set forth in SEQ ID NO:473 of Ross ('799). This is because Madden et al. teach the identifying characteristics of at least two cysteine proteases that are encoded by *P. gingivalis* genomic DNA sequences and specifically provide a basis for further identification of related cysteine proteases of *P. gingivalis* in their Fig. 7 wherein the deduced amino acid sequences of the active center regions of the *P. gingivalis* prtT product differ at only seven positions among the corresponding forty-six amino acid regional sequences at positions 188 through 203 (positions 189, 199 and 200) and 334 through 361 (positions 334, 344, 345, and 358) of the deduced amino acid sequence of the DNA sequence set forth in SEQ ID NO:473 of Ross ('799) while the *tpr* gene product's deduced amino acid sequence differs at twenty-one positions among the deduced amino acid sequences of the corresponding active center regions of the *P. gingivalis* prtT product.

It would further have been obvious to one of ordinary skill in the art at the time the invention was made to practice the methods of claims 27 and 28 with a cysteine protease identified according to teachings of Madden et al. as encoded by the *P. gingivalis* genomic DNA sequence set forth in SEQ ID NO:473 of Ross ('799). This is because Chen et al. teach that several protease inhibitors should be assayed to identify those which inhibit a *P. gingivalis* cysteine protease that "can degrade [an] α_1 proteinase inhibitor[ ]", a serpin and because Nelson et al. teach that the α_1-proteinase inhibitor should be used in an assay to detect proteolytic activities of *P. gingivalis* proteases, which may include cysteine proteases, that cleave the reactive site loop of this key serpin component of the host defense system.

Allowable Subject Matter

Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. It is also noted that a claim describing a generic nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1, a claim that specifically describes a polypeptide having the amino acid sequence of SEQ ID NO:1, and claims that specifically describe fragments of the amino acid sequence of SEQ ID NO:1 having the sequences from position 148 through position 629, inclusive, and from position 148 through position 843, inclusive, and methods of identifying inhibitors of cysteine proteases having these discrete amino acid sequences would be free of the prior art of record. This is because the prior art neither discloses nor suggests that the 684-amino acid polypeptide encoded by SEQ ID NO:473 of Ross ('799) extends for a further 159 amino acids or that it should be truncated to provide an active cysteine protease having an amino terminus at position 148, and truncated to provide a carboxyl terminus at position 629, thereof.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Fletcher et al., 1994, cited by Madden et al., disclose the deduction of the

amino acid sequence of the product of the *P. gingivalis prt*H gene, Fig. 4, and its identification as a cysteine protease on the basis of regional sequence homologies, Fig. 6, as well as the identification of several host protein substrates and the need for identification of further host protein substrates, page 4284. Bedi et al., 1994, cited by Madden et al., disclose the isolation and identification of a *P. gingivalis* cysteine protease that "possesses the ability to inactivate several components of [the] host defense system", including, page 605, the serpin α_1-trypsin inhibitor, which is "digested by [the] purified protease", Fig. 9, lane 6+, wherein the serpin was cleaved in a non-denatured state prior to loading on the gel, see legend to Fig. 9.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 703.308.3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. The examiner's direct fax phone number is 703.746.3169. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
June 25, 2003